STENT AND METHOD FOR DRUG DELIVERY FROM STENTS

Technical Field

The present invention relates to implantable devices, such as stents, used for implantation in tissue for cardiovascular intervention and other purposes and the delivery of drugs placed on or in the stent. In particular, the present invention relates to a stent prepared to deliver drugs when heated by electromagnetic fields and a method and system for causing drug-coated or drug-loaded stents to deliver their drugs into the blood stream of a cardiovascular vessel or into surrounding tissue.

Background of the invention

Different techniques are known to prevent in-stent restenosis of cardiovascular or other stents. In-stent restenosis affects nearly 50% of all stenting procedures. Known techniques to prevent in-stent restenosis are the use of radioactive stents (brachytherapy), biodegradable stents, drug-coated stents and inductive heating of stents.

Stents can be coated or loaded with different drug formulations, including materials such as biologically active micro-spheres used for controlled release of biologically active agents inhibiting restenosis of the stent. These drugs can be included in encapsulations such as polyethylene glycol substances that are formulated to dissolve within a period of time to release the biologically active micro spheres into the vessel wall of the organ or the vessel in which the stent is located.

One problem with these drug-coated and drug-loaded stents is that the dissolving or eluting mechanism of the drug is not controllable or selectable by the physician. Whatever time release is designed into the drug coating or loading, together with conditions within the patient, will cause the drug to be delivered in a manner that cannot be controlled or selected once the coated or loaded stent is inserted. Thus, the drug effect will continue to run its

course. If the drug is designed to have an inhibiting effect on tissue growth, that effect may go too far and actually be deleterious to the tissue. This problem is addressed by this invention.

Summary of the Invention

An object of the present invention is to provide a mechanism for controlling the delivery or activity of a drug placed on or in a drug-delivery stent and to provide such control non-invasively from outside the patient's body. In German Gebrauschmuster DE 295 19 982.2 and in European patent application EP 1 036 574 A1 inductive or hysteresis-loss methods for heating up stents non-invasively with electromagnetic fields have been presented. The stated purpose of this heating is to prevent or retard cell growth in the regions adjacent the stent. The heating of the stent is contemplated to be sufficient to render the cells adjacent the stent non-viable.

During inductive heating as described in, e. g., patent DE 295 19 982.2 the stent heats up from normal body temperature of 37.6°C to higher temperatures, typically above 40°C. The heat energy can then be used in several different ways to control activity of a drug that is coated on or loaded in a stent. First, the heat within a stent can be used to activate a heat-sensitive drug-releasing material (e.g., a fiber) from which the stent is made. The heat thus makes available a drug that is otherwise captured within the stent material and is wholly or largely not available for activity with adjacent tissue. With a properly-selected drug-releasing material, the opposite effect is also possible, i.e., that heat deactivates the material or prevents or inhibits release. Second, the heat within the stent is conducted by thermal heat conduction to the outer surface of the stent. If a drug coating is at that surface, the heat can be used to activate a drug that is wholly or largely inactive at normal body temperatures. Alternatively, if the drug is contained in a heat-sensitive release coating that is on the stent surface, the heat energy at the stent surface can cause the drug to be released, so that it can

diffused or dissolved into adjacent tissue. Again, with a properly selected drug formulation, heating to cause drug deactivation or inhibition of drug release is also possible. Third, as the heat energy at the stent surface travels by heat conduction into the tissue adjacent the stent, the proteins and other molecules in the tissue will also become heated. Thus, not only is the drug released, but the microenvironment in which the drug and adjacent tissue interact will be heated. This heating may enhance or otherwise affect the drug-tissue reactions in ways that are not present when one or both are at lower temperatures.

In one particular embodiment, the drug coated on or loaded in the stent is a restenosis-preventing drug. According to the above possibilities, the drug can be released by elevated temperatures from within or at the surface of the stent, it can be activated (or deactivated) by elevated temperatures at the stent surface and/or the drug-adjacent tissue reaction can be enhanced by elevated temperatures in the stent or at its surface and also in the adjacent tissue.

The present invention uses the stent heating method to provide control over delivery of one or more drugs from a drug-coated or drug-loaded stent. The dissolution and/or dispersion of a drug is usually a function of temperature. The higher the temperature is, the faster the drug will dissolve or disperse into the surrounding medium from the surface where it is placed. Duration of the elevated temperature also plays a role in increasing the amount of drug delivered.

According to the present invention, a stent can be made for selective drug delivery by placing the drug to be delivered onto the stent in such a way that it is encapsulated in a release layer, or the drug can be coated on the stent directly without such a layer. In the latter case, the drug on the stent is not removed from encapsulation by heating. Rather it is selected and/or formulated so that it has its active effect when it and/or the surrounding tissue is at or above an elevated threshold temperature; when the drug and/or the surrounding tissue is below the elevated threshold temperature, the drug has no active effect.

Although stents prepared with variety of drugs that can be delivered in this way are possible, one application is a stent bearing a drug that would help prevent restenosis from occurring. We propose a stent to deliver or activate a restenosis-preventing drug. The drug may be located directly on the surface of the stent or within the stent or inserted in an encapsulation layer on the surface of the stent. In all cases the stent-carried drug will not be available or be active at body temperature, but it becomes available or active at a certain temperature point above body temperature. (The reverse effect of a drug active at body temperature and selected to become inactive is also possible and may be useful.)

The invention also involves a treatment method. In order to make the drug available or active at the stent surface, the stent with the drug has to be heated. The patient will come to the hospital in a defined sequence to be treated for a certain period of time with stent heating to certain temperatures selected based on the drug and/or its encapsulation and/or the drug-tissue interaction at various layers. The drug then will be delivered into or at the patient's blood or vessel wall.

Therapeutic agents to inhibit restenosis have been used with varying success. Kunz et.al. disclosed in US-5,733,925 that Taxol, an antimicrotubule agent isolated from the bark of the western Pacific Yew tree, is especially effective in combating restenosis. Taxol may also prevent thrombus formation. Systemic administration of Taxol can have undesirable side effects, making local administration a preferred mode of treatment. Therefore Taxol and its derivates can only be given in small quantities.

Brief Description of the Drawings

Figure 1 is a schematic, cross-sectional view of a stent with a layer of encapsulated drug material on the stent surface.

Figure 2 is a schematic, cross-sectional view of a stent with drug layer that is on the stent surface and not encapsulated.

Figure 3 is a schematic, cross-sectional view of a stent with drug material captured within the stent material.

Figure 4 demonstrates various layers of coatings and their behaviour in eluting of drugs over temperature.

Figure 5 demonstrates various layers of coatings and their behaviour in eluting of drugs over temperature.

Figure 6 demonstrates various layers of coatings and their behaviour in eluting of drugs over temperature.

Figure 7 demonstrates different coatings on the end of the stent.

Detailed Description of the Preferred Embodiments

Figure 1 shows an embodiment of the invention. A thin-walled stent 20 of generally cylindrical shape is shown inserted within tissue, where such tissue may be the interior of a blood vessel with opposing walls 10 enclosing the stent 20. On the exterior of the stent 20 is a layer of drug material 40, which is in direct contact with the tissue 10. (In reality, the stent 20 will normally be woven wires or a grid of some kind; thus, the "exterior" of the stent 20 is not solely the outer surface of the cylindrical form of the stent, but also includes other portions of the stent 20 that contact the tissue 10, whether these are on the outer surface of the cylindrical form or the inner surface or interstitial surfaces in between the two.) In this embodiment, the drug material 40 comprises an active drug dispersed in an encapsulation

material that prevents the active drug from having effective contact with the tissue 10 at normal body temperatures. However, at elevated temperatures, the encapsulation material that is part of the drug material 40 breaks down to release the active drug and permit molecules of the active drug to interact with molecules of the tissue 10.

For example, the active drug can be a restenosis-preventing drug. The restenosis preventing drug is inserted into or encapsulated in a biodegradable polymer, such as a polyethylene glycol composition, to form the drug material layer 40. The stent 20 is then heated at a temperature of 39°C and the biodegradable polymer dissolves. This makes the drug available to contact or interact with the tissue 10 surrounding the stent 20. In fact, the drug will in most cases diffuse somewhat into the surrounding tissue, thus making its active effect available not only at the exterior of the stent 20, but also at small distances therefrom. Preferably, the heating is applied non-invasively. This can be done by a radio frequency generator device that generates an electromagnetic field sufficient to cause inductive (and/or hysteresis loss) heating in the stent. Such devices are described in Gebrauchsmuster DE 295 19 982. 2 and in European patent application EP 1 036 574 A1. When the inductive heating treatment is turned off, the stent 20 will cool down to normal body temperature and the heat-activated process stops. This procedure can be repeated several times. (As noted above, the opposite effect is also possible, i.e., that heat deactivates the material or prevents or inhibits release.) As long as the supply of the drug material is not exhausted, more of the encapsulation layer will break down and more of the active drug will be released.

Another embodiment is shown in Figure 2. A thin-walled stent 120 of generally cylindrical shape is shown inserted within tissue, where such tissue may be the interior of a blood vessel with opposing walls 110 enclosing the stent 120. On the exterior of the stent 120 is a layer of drug material 140, which is in direct contact with the tissue 110. (In reality, the stent 120 will normally be woven wires or a grid of some kind; thus, the "exterior" of the stent 120 is not solely the outer surface of the cylindrical form of the stent, but also includes other

portions of the stent 120 that contact the tissue 110, whether these are on the outer surface of the cylindrical form or the inner surface or interstitial surfaces in between the two.) In this embodiment, the drug material 140 comprises an active drug that is formulated so that it has substantially no effect on the tissue 110 at normal body temperatures. However, at elevated temperatures, the active drug undergoes a change that makes it active. Thus, the previously substantially inert molecules of the active drug begin to interact with molecules of the tissue 110. (As noted above, with a properly selected drug formulation, heating to cause drug deactivation or inhibition of drug release is also possible.) This effect can be achieved by heating that causes changes in the activity level of either the active drug with which the stent is coated or by changes in the activity level of proteins or other molecules in the tissue 110 with respect to the active drug. That is, heating may have an effect on the reaction speed or nature of the interaction of the active drug and the tissue 110 at the drug-adjacent tissue interfaces.

A further embodiment is shown in Figure 3. A stent 220 of generally cylindrical shape is shown inserted within tissue, where such tissue may be the interior of a blood vessel with opposing walls 210 enclosing the stent 220. The walls 240 of the stent 220 are impregnated or loaded with drug material, which is mainly not in direct contact with the adjacent tissue 210. In this embodiment, the drug-loaded walls 240 contain an active drug that is formulated into the wall material so that it has substantially no effect on the adjacent tissue 210 at normal body temperatures. However, at elevated temperatures, the active drug is released from within the walls 240. Thus, the previously substantially unavailable molecules of the active drug begin to interact with molecules of the adjacent tissue 210. This effect can be achieved by heating that causes changes in the binding of the active drug with which the stent is loaded or by actual dissolution of the walls 240 loaded with the active drug. That is, heating may have an effect on the release of the active drug from the walls 240 or the integrity of the walls

240. In either event, the heating of the stent causes increased availability of the active drug at the drug-adjacent tissue interfaces.

Examples

The herewith claimed method of heating stents to heat a drug layer applied to the stent and heat surrounding tissue may help other drug delivery techniques to deliver their drugs in a controllable or selective way.

Examples are:

In U. S. patent 5,980,566 an iridium oxide coating for a stent has a biodegradable carrier of drugs applied thereto for beneficial localized action, as by incorporating into the carrier along the inward-facing surface an anticoagulant drug to reduce attachment of thrombi with blood flow through the lumen of the stent. Heat delivered through the method as claimed here could selectively enhance drug release or availability to help the process to reduce the attachment of thrombi with blood flow through the lumen of the stent.

In U.S. patent 5,980,551 (see also PCT application WO98/34669) a stent has biologically active micro spheres that release a biologically active agent into the vessel wall or organ. To inhibit restenosis of the stent the biologically active micro spheres include encapsulated PGE1 in a water soluble polyethylene glycol mix. The temperature increase process as described here could help selectively control the period of time to dissolve and release the PGE1 into the vessel wall or organ.

In the U.S. patent 5,980,551 an anti-coagulation drug is incorporated into a biodegradable material to form a liquid-coating material. The temperature process as described in the present invention could help to continue this integrated coating which is less than about 100 microns.

In the application described in U.S. patent No. 5,733,327 the temperature elevating process described in the present invention could help selectively control the dissolution mechanism of poly-e-caprolactone, poly-D, L-deca—lactone, poly-dioxane and copolymer.

In the application described in U.S. patent No. 5,700,286 the process as described in the present invention could help enhance effectiveness for the lubricious material, which can be polyethylene, oxide, polyethylene glycol, polyethylene acetate, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylamide, hydrophilic soft segment urethanes, some natural gums, polyanhydrides or other similar hydrophilic polymers, and combinations thereof.

In the application described in PCT patent WO 00/56376 the temperature method as described in the present invention could help selectively degrade devices formed of polyhydroxylkanoates. These are taught as used in conjunction with metal that can be inductively heated.

In the application described in German patent application DE 197 37 021 A1 the method as described in the present invention could help selectively oxidize the medical implant which is made of magnesia, iron or zinc or other suitable materials.

In the application described in PCT application WO 96/33757 the temperature treatment of the present invention could help selectively control the process of dissolving the surface coating with a physiological acceptable polymer, such as polyvinyl alcohol or fibrinin, containing dissolved or dispersed therein a nitroso compound, such as 2-metyhyl-2-nitrosopropane.

In the application described in German patent application DE 195 14 104 A1 the method as described in the present invention could support the selective dissolution of the drug such as poly-D, L-lactide, thrombine inhibitors and other derivates.

Inductive Heating

Heating of stents as contemplated by this invention can be performed with metallic stents having adequate magnetic permeability or field absorbing qualities according to the teachings of German Gebrauchsmuster DE 295 19 982. 2 and European patent application EP 1 036 574 A1. (The disclosures of these are incorporated by reference.) In these, electromagnetic fields are generated at a coil or other sending antenna and the stent is placed in the field with an orientation and at a distance and location that permit sufficient power to be absorbed at the stent (acting as a receiving antenna), such that heat can be generated in the stent. The amount of heat energy delivered to stent and the duration of heating are important variables for the drug activity selective control contemplated by this invention. The electromagnetic energy may be provided in controlled, brief pulses to permit a more precise control of the energy delivered to the stent and resulting heating effects. The greater the control of heating, the greater the control of the resulting drug release, or drug activation or drug-adjacent tissue reaction enhancement.

As used herein, a "stent" is any implantable device that provides some support or structure to surrounding tissue. Thus, the invention is applicable to a variety of stents or supporting implantable devices, not just those that are used in blood vessels. As used herein, a "drug" means a substance that has therapeutic effect, which may include gene therapy formulations as well as more conventional drugs based on chemical formulations or biological derivatives.

It is appreciated that besides stents, any other type of suitable implantable devices can be used within the scope and spirit of the present invention to controllably elute a drug off of an implantable device. Also, the implantable devices may be used just for the purpose of eluting drugs into the body. One of such implantable devices may be a metallic hip joint which is coated with a drug for better biocompatibility. The drug may be eluted by temperature. Also, a device may be made as a ball shaped type or as many small pills which are implanted just to be heated inductively to elute the drug.

It is also appreciated that the devices can be temporarily implanted or permanently implanted. These device may be used to help chemotherapy or any other therapy.

One exemplary application can be to implant a metallic coil or pellet in the patient's prostate and use the above described invention to control the elution of a drug to treat a prostate disease. Other exemplary applications may be to control the elution of insulin off of an implantable device in a diabetic patient, or to control the elution of a drug off of an ophthalmic device in the eye to treat vision related diseases.

Accordingly, the present invention provides an implantable device having at least one coated drug material capable of being heated inductively and delivering the drug material to a body when heated. The frequency of the inductive heat is preferably below 1 MHz. Under 1 MHz, the body tissue is generally opaque for radio frequency inductive heating, above that frequency the body tissue absorbs the energy and is heated itself.

While the present invention has been described with reference to several embodiments thereof, those skilled in the art will recognize various changes that may be made without departing from the spirit and scope of the claimed invention. For example, implantable devices can be energized by inductive heating, radio or microwave frequency and tissue transmitting light technology, etc. It is noted that light of certain lower wavelength can travel further into tissue than light of a higher wavelength and, therefore, is absorbed deeper in the tissue. This effect can be used to absorb the light deeper to heat up implants deeper in the tissue. Accordingly, this invention is not limited to what is shown in the drawings and described in the specification but only as indicated in the appended claims, nor is the claimed invention limited in applicability to one type of drug. Any numbering or ordering of elements in the following claims is merely for convenience and is not intended to suggest that the ordering of the elements of the claims has any particular significance other than that otherwise expressed by the language of the claims.

The elution process itself at this point in research does not seem to be clearly understood and it seems that it is more a dissolving mechanism with an out-diffusion of the drug through the coating matrix. Hence, the elution process might also be called the dissolving of the coating. It seems that the physics behind the elution process can be the theory of dissolving. Hence, the factor in the differential equations describing the elution-process are factors to dissolve or factors of dissolving or dissolving-coefficients. There might also be the process of out-diffusion of a drug of a matrix which later stays when the drug has diffused out or might itself be biodegradable and dissolves.

The temperature graphs of figures 4 to 7 is are normed to body temperature, meaning that the zero-point of the x-axis is actually body temperature.

In figure 4a is shown the cross sectional view of a stent strap 1 with a drug coating 2. Coating 2 might be a matrix carrier with taxol or a taxol derivate or it might be the drug itself. The taxol or taxol derivate drug, or the drug is to dissolve. The dissolving of the drug can be enhanced by temperature. Figure 4b shows the dissolving of the drug over temperature. Shown id the logarithm of the dissolved amount of drug over temperature. The dissolving-coefficient $D_2(T)$ of the coating 2 might be a function of temperature itself and hence was written as if it would be. This dependence of temperature of the coefficient might might be so small and almost zero that $D_2(T) = D_2 = \text{constant}$.

Figure 4c shows a stent strap 1 with a dissolving-drug-layer 3 and a diffusion barrier-layer 4 and figure 4d shows the amount of dissolving drug D over temperature. The diffusion barrier 4 stops the drug coating 3 of dissolving. When the temperature rises the diffusion layer allows the drug to pass through resulting in the coefficient $D_4(T)$ for the whole system. The coefficient is now temperature dependent, since the diffusion part of it is and hence the

overall coefficient is as well. Again, the drug layer 3 might be the coated pure drug itself or might be a drug in a matrix. Above a threshold temperature T_T the drug will dissolve in the surrounding of the stent.

Figure 4 e shows a stent stap 1 with drug coating 5, a first diffusion barrier6 and a second diffusion barrier 7. First diffusion barrier 6 works as the one of the example of figure 4 c and figure 4 d. Second diffusion barrier 7 is different in type, it will let less drugs pass when heated, hence it will shut down. If diffusion barriers 6 and 7 are laid out property, the dissolving of the whole layer structure will allow the elution of the drug only in a defined temperature window between T_{T6} and T_{T7} as indicated in figure 4f.

Figure 5 shows the same mechanism as of figure 4 for a stent material with a Curie temperature. The Curie temperature of the stent material will only allow the stent to heat up to a defined maximum temperature. If a palladium-cobalt alloy is chosen, this maximum temperature can be chosen by the alloy mixture to be between 45°C and 65°C and hence there is no danger of overheating the stent. The dissolving amount of drug above the Curie temperature will than be constant as shown in figure 5b, 5d, and 5f. Figure 5g shows represents a graph of the magnetization M of the stent material over temperature. Above the Curie temperature T_C the material can not be further magnetized and heated.

Figure 6a represents a case in which a the stent strap 1 is coated with a drug coating 8, a diffusion barrier 9 and a second drug layer 10. The elution behaviour of the system is shown in figure 6b. At body temperature only the second drug containing layer dissolves. This process is being enhanced when temperature is increased. Diffusion barrier 9 allowes the drug of layer 8 to pass when the threshold temperature T_T is reached. Hence, with temperature we increase the overall drug dissolving further. Layer 8 and 10 might carry the same or different

drugs. Figure 6c and 6d represent the same case except that a second diffusion barrier 11 was coated on the overall outside.

Figure 7 shows an example in which different layer systems are used over the entire stent 12. At the blood inflow side of the stent 12, arrow 17 indicated the blood flow, a drug coating with a fast coefficient of dissolving and no diffusion barrier was chosen to overcome an edge effect. In the middle body part 14 of the stent 12 a drug coating with diffusion barrier was chosen to result in a slow dissolving above a threshold temperature $D_{14}(T)$. the other end 16 carries a drug coating as on the first end with diffusion barrier, so that the dissolving starts at elevated temperatures. Different other layer systems can be thought of to give different dissolving or drug eluting characteristics.

NUMBERS

1 cross sectional view of a stent strap

2 single layer coating, containing the drug (substrate matrix plus drug)

3 coating containing the drug (substrate matrix plus drug)

4 diffusion barrier coating

5 coating containing the drug (substrate matrix plus drug)

6 diffusion barrier coating

7 coating containing the drug (substrate matrix plus drug)

8 coating containing the drug (substrate matrix plus drug)

9 diffusion barrier coating

10 drug layer

11 diffusion barrier coating

12 stent (three dimensional view)

13 inner lumen of stent 12

14 coating of the stent 12 of slow dissolving $D_{14}(T)$ of a drug

15 coating on proximal end of stent 12 with fast dissolving $D_{15}(T)$ of a drug

16 coating on distal end of stent 12 with fast dissolving $D_{16}(T)$ of a drug

17 blood flow direction